Entecavir

Brand Name: Baraclude
Drug Class: Opportunistic Infection and Other Drugs

Drug Description

Entecavir is a guanosine nucleoside analogue with selective activity against hepatitis B virus (HBV). [1]

HIV/AIDS-Related Uses

Entecavir was approved by the FDA on March 30, 2005. Oral entecavir is indicated in the treatment of HBV infection, a common coinfection in individuals infected with HIV.[2]

Non-HIV/AIDS-Related Uses

Entecavir is indicated for the treatment of chronic HBV infection in adults with evidence of active viral replication and evidence of either persistent elevations in serum aminotransferases (ALT or AST) or histologically active disease.[3]

The FDA based its approval of entecavir on the results of 3 studies that compared entecavir to lamivudine, another drug used for the treatment of HBV. In all 3 studies, patients treated with entecavir showed significant improvement in the liver inflammation caused by HBV and an improvement in the degree of liver fibrosis (scarring). In addition, a higher percentage of patients treated with entecavir showed significant overall improvement compared to lamivudine.[4]

Pharmacology

Entecavir is efficiently phosphorylated to the active triphosphate form, which has an intracellular half-life of 15 hours. By competing with the natural substrate deoxyguanosine triphosphate, entecavir triphosphate functionally inhibits all three activities of HBV polymerase: base priming, reverse transcription of the negative strand from the pregenomic messenger RNA, and synthesis of the positive strand of HBV DNA.[5]

Entecavir has not been fully evaluated in human trials. In one randomized, double-blind, placebo-controlled study, entecavir was compared to placebo in 68 patients coinfected with HIV and HBV who experienced recurrence of HBV viremia while receiving a lamivudine-containing highly active antiretroviral therapy (HAART) regimen. Patients continued their lamivudine-containing HAART regimen (lamivudine dose 300 mg/day) and were assigned to add either entecavir 1 mg once daily (51 patients) or placebo (17 patients) for 24 weeks, followed by an open-label phase for an additional 24 weeks, in which all patients received entecavir. At baseline, patients had a mean serum HBV DNA level by PCR of 9.13 log10 copies/ml. The median HIV RNA level remained stable at approximately 100 copies/ml through 24 weeks of blinded therapy. There are no data in patients with HIV/HBV coinfection who have not received prior lamivudine therapy.[6]

Following oral administration in healthy volunteers, entecavir peak plasma concentrations (Cmax) occurred between 0.5 and 1.5 hours. Following multiple daily doses ranging from 0.1 to 1 mg, Cmax and area under the concentration-time curve (AUC) at steady state increased in proportion to dose. Steady state was achieved after 6 to 10 days of once-daily administration with approximately twofold accumulation. For a 0.5 mg oral dose, Cmax at steady state was 4.2 ng/ml and trough plasma concentration (Cmin) was 0.3 ng/ml. For a 1 mg oral dose, Cmax was 8.2 ng/ml and Cmin was 0.5 ng/ml. In healthy volunteers, tablet bioavailability was 100% relative to the oral solution; the oral solution and tablet may be used interchangeably.[7]

Oral administration of entecavir 0.5 mg with a standard high-fat meal (945 kcal, 54.6 g fat) or a light meal (379 kcal, 8.2 g fat) resulted in delayed absorption (1.0 to 1.5 hour fed vs. 0.75 hours fasted), a decrease in Cmax of 44% to 46%, and a decrease in AUC of 18% to 20%.[8]

Based on the pharmacokinetic profile of entecavir after oral dosing, the estimated apparent volume of distribution is in excess of total body water, suggesting that entecavir is extensively distributed into tissues.[9]

Entecavir is in FDA Pregnancy Category C. There are no adequate and well-controlled studies in pregnant women. Reproduction studies have been

Pharmacology (cont.)

performed in rats and rabbits at orally administered doses of 200 and 16 mg/kg/day and showed no embryotoxicity or maternal toxicity in rat and rabbit at doses producing systemic exposures approximately 28 and 212 times those achieved at the highest recommended dose of 1 mg/day in humans. In rats, maternal toxicity, embryo-fetal toxicity (resorptions), lower fetal body weights, tail and vertebral malformations, reduced ossification (vertebrae, sternebrae, and phalanges), and extra lumbar vertebrae and ribs were observed at exposures 3,100 times those in humans. In rabbits, embryo-fetal toxicity (resorptions), reduced ossification (hyoid), and an increased incidence of 13th rib were observed at exposures 883 times those in humans. In a peri-post-natal study, no adverse effects on offspring were seen with entecavir administered orally to rats at exposures greater than 94 times those in humans. Because animal reproduction studies are not always predictive of human response, entecavir should be used during pregnancy only if clearly needed and after careful consideration of the risks and benefits. To monitor fetal outcomes of pregnant women exposed to entecavir, an Antiretroviral Pregnancy Registry has been established. Healthcare providers are encouraged to register patients online at http://www.APRegistry.com or by calling 1-800-258-4263.[10]

Entecavir is excreted into the milk of rats. It is not known whether this drug is excreted in human milk. Mothers should be instructed not to breastfeed if they are taking entecavir. There are no studies in pregnant women and no data on the effect of entecavir on the transmission of HBV from mother to infant. Appropriate interventions should be used to prevent neonatal acquisition of HBV.[11]

Binding of entecavir to human serum proteins in vitro is approximately 13%.[12]

After reaching peak concentration, entecavir plasma concentrations decrease in a biexponential manner, with a terminal elimination half-life of approximately 128 to 149 hours. The observed drug accumulation index is approximately twofold with once-daily dosing, suggesting an effective accumulation half-life of approximately 24 hours.[13]

Following administration of 14C-entecavir in humans and rats, no oxidative or acetylated metabolites were observed. Minor amounts of phase II metabolites (glucuronide and sulfate conjugates) were observed. Entecavir is not a substrate, inhibitor, or inducer of the cytochrome P450 (CYP450) enzyme system.[14]

Entecavir is predominately eliminated by the kidney, with urinary recovery of unchanged drug at steady state ranging from 62% to 73% of the administered dose. Renal clearance is independent of dose and ranges from 360 to 471 ml/min, suggesting that entecavir undergoes both glomerular filtration and net tubular secretion.[15]

The pharmacokinetics of entecavir following a single 1 mg dose were studied in patients without chronic hepatitis B infection with selected degrees of renal impairment, including patients whose renal impairment was managed by hemodialysis or continuous ambulatory peritoneal dialysis (CAPD). Dosage adjustment is recommended for patients with a creatinine clearance of less than 50 ml/min, including patients on hemodialysis or CAPD. Following a single 1 mg dose of entecavir administered 2 hours before hemodialysis, approximately 13% of the entecavir dose was removed by hemodialysis over 4 hours. Entecavir should be administered after hemodialysis. CAPD removed approximately 0.3% of the dose over 7 days.[16]

The coadministration of HIV nucleoside reverse transcriptase inhibitors (NRTIs) with entecavir is unlikely to reduce the antiviral efficacy of entecavir against HBV or of any of these agents against HBV. In HBV combination assays in vitro, abacavir, didanosine, lamivudine, stavudine, tenofovir, and zidovudine were not antagonistic to the anti-HBV activity of entecavir over a wide range of concentrations. In HIV antiviral assays, entecavir was not antagonistic to the in vitro anti-HIV activity of these NRTIs at greater than 4 times the Cmax of entecavir.[17]

Cross resistance has been observed among HBV nucleoside analogues. In cell-based assays

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Pharmacology (cont.)

entecavir had 8- to 30-fold less inhibition of replication of HBV that contained lamivudine resistance mutations rtL180M and rtM204V/I than of wild-type virus. Recombinant HBV genomes encoding adefovir resistance substitutions at either rtN236T or rtA181V remained susceptible in vitro to adefovir but retained resistance to lamivudine.[18]

Adverse Events/Toxicity

The most common adverse effects with at least a possible relation to entecavir in clinical studies were headache, fatigue, dizziness, and nausea.[19]

A large post-marketing study of entecavir will be conducted by the manufacturer to evaluate the risks of cancer and liver-related complications.[20]

Drug and Food Interactions

Entecavir should be taken on an empty stomach, at least 2 hours after a meal and 2 hours before the next meal.[21]

Because entecavir is primarily eliminated by the kidneys, coadministration of entecavir with drugs that reduce renal function or compete for active tubular secretion may increase serum concentrations of either entecavir or the coadministered drug. The effects of coadministration of entecavir with other drugs that are renally eliminated or are known to affect renal function have not been evaluated, and patients should be monitored closely for adverse effects when entecavir is coadministered with such drugs.[22]

Coadministration of entecavir with lamivudine, adefovir dipivoxil, or tenofovir disoproxil fumarate did not result in significant drug interactions.[23]

Contraindications

Entecavir is contraindicated in patients with previously demonstrated hypersensitivity to entecavir or any component of the product.[24]

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues alone or in combination with antiretrovirals. Severe acute exacerbations of hepatitis B have been reported in patients who have discontinued anti-hepatitis B therapy, including entecavir. Hepatic function should be monitored closely with both clinical and laboratory follow-up for at least several months in patients who discontinue anti-hepatitis B therapy. If appropriate, reinitiation of anti-hepatitis B therapy may be warranted.[25]

Clinical Trials

For information on clinical trials that involve Entecavir, visit the ClinicalTrials.gov web site at http://www.clinicaltrials.gov. In the Search box, enter: Entecavir AND HIV Infections.

Dosing Information

Mode of Delivery: Oral.[26]

Dosage Form: Film-coated, triangular-shaped tablets containing 0.5 or 1.0 mg entecavir.[27]

Oral solution containing 0.05 mg/ml entecavir in a 260 ml bottle.[28]

Storage: Store entecavir tablets in a tightly closed container at 25 C (77 F); excursions are permitted between 15 C and 30 C (59 F and 86 F).[29]

Store entecavir oral solution in its outer carton at 25 C (77 F); excursions are permitted between 15 C and 30 C (59 F and 86 F).[30]

Chemistry

CAS Name: 6H-Purin-6-one,2-amino-1, 9-dihydro-9-[(1S,3R,4S)-4-hydroxy-3-(hydroxymethyl)-2-methylenecyclopentyl]-monohydrate[31]

CAS Number: 142217-69-4[32]

Molecular formula: C12-H15-N5-O3 x H2O[33]

C48.80%, H5.81%, N23.72%, O21.67%[34]

Molecular weight: 295.29[35]

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Further Reading

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For More Information

Contact your doctor or an AIDSinfo Health Information Specialist:

• Via Phone: 1-800-448-0440 Monday - Friday, 12:00 p.m. (Noon) - 5:00 p.m. ET

• Via Live Help: http://aidsinfo.nih.gov/live_help Monday - Friday, 12:00 p.m. (Noon) - 4:00 p.m. ET

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